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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

A New Positive Feedback Circuit in the Fibrosis–Cancer Axis for Male Livers

Serotonin (also known as 5-hydroxytryptamine [5-HT]) is a small-molecule neurotransmitter that was identified in a series of studies conducted between 1935 and 1953 because of its capacity to induce contractions in the intestine and blood vessels. A plethora of functions for the serotonin system have been described, including regulation of mood, blood clotting, gut motility, systemic energy homeostasis, and tissue repair. Serotonin is synthesized from the essential amino acid tryptophan via tryptophan hydroxylase (TPH) in the brain and enterochromaffin cells of the gastrointestinal tract. Gut-produced serotonin then actively is taken up by platelets and travels in the blood stream where it can be released on demand.

Seminal studies in the past decade have identified several important roles for the serotonin system in liver homeostasis and disease. An elegant study in 2006 introduced a new paradigm for platelet-derived serotonin in promoting liver regeneration by acting directly on hepatocytes (via the hepatocyte 5-HT_{2A} receptor).[1] A subsequent study in 2011 established a more complex model, showing the antiregenerative and profibrogenic function of serotonin in normal and diseased liver through 5-HT_{2B} receptor activation in stellate cells and production of transforming growth factor (TGF)-β1.[2] These studies described an integral role for the serotonin system in controlling the balance between hepatic regeneration and fibrosis. Given that inflammation and fibrosis provide a permissive microenvironment for the emergence of tumorigenic hepatocytes and that hepatocellular carcinoma is the third-leading cause of cancer death with a poor prognosis and very limited therapeutic options, a key follow-up study was to interrogate the role of serotonin-related pathways in the development of hepatocellular carcinoma in models with progressive liver fibrosis. This is even more important in light of recent findings about the reliability of serum serotonin as a potential clinical biomarker for the diagnosis and staging of liver cancer.[3]

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Yang et al have described[4] a new positive feedback circuit for serotonin system components in fueling the fibrosis–cancer axis in diseased liver.[4] The authors also have reported that this loop is essential for sexual dimorphism in liver cancer.[4] To investigate this topic, they used a transgenic zebrafish model with the $kras^{V12}$ mutation and showed accelerated fibrosis and cancer in males. Subsequently, through a series of pharmacologic interventions, they discovered a 2-way intercellular communication loop between hepatocytes and activated stellate cells during the progression of liver disease. In this circuit, hepatocytes produce serotonin via up-regulation of TPH1. The induced serotonin stimulates activated stellate cells via the 5-HT_{2B} receptor, inducing TGF-β1 synthesis. The production of TGF-β1 in this model further promotes stellate cell activation, fibrosis, and carcinogenesis. Strikingly, 5-HT_{2B}-receptor–induced TGF-β1 signals back to hepatocytes, stimulating them to up-regulate TPH-1 and serotonin synthesis further. Hence, the 2-way intercellular cross-talk acts as a positive feedback loop to maintain or enhance the phenotype of both hepatocytes and stellate cells. The investigators discovered that several components of this circuit (eg, TPH-1, serotonin, 5-HT_{2B} receptor, and TGF-β1) are increased in the liver of male fish. When they studied samples from human patients, they found similar sexual dimorphism in both serotonin and TGF-β1, especially in inflammation and cirrhosis samples.

Similar to every interesting study, this one raises several new questions. For example, it is not obvious what factor(s) turn on the circuit in an injured liver in a sex-dependent fashion. In addition, we do not know which cell type (stellate cells or hepatocytes) begins the cross-talk. We do know that estrogen inhibits interleukin 6 production by Kupffer cells, which results in a reduced cancer risk in females.[5] One intriguing possibility is that the serotonin feedback loop cooperates with inflammatory signaling molecules such as interleukin 6 and acts as a signal amplifying circuit to further increase sex disparity in liver cancer. In fact, several studies have shown cross-talk between the serotonin system and inflammatory pathways including Toll-like receptors. Until now, it was thought that platelets were the key players in serotonin release in injured liver, and gut-produced serotonin was the main source. This study argues that intrahepatic serotonin synthesis may be equally important.

Potent and selective pharmacologic agents that target the serotonin system are already in the clinic. 5-HT_{2B} antagonists are being studied as treatments for several conditions including pulmonary hypertension and chronic heart disease.[6] Therefore, this class of drug may provide an attractive option for controlling the fibrosis–cancer axis in human liver disease. However, it still is unclear at what stages of disease in human beings it would be most effective to target the serotonin system. Regardless, the article by Yang et al[4] provides us with important evidence that the serotonin system is a key player in liver fibrosis and cancer, and they identify it as an important therapeutic target that is worthy of further investigation.

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Conflicts of interest
The author discloses no conflicts.

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